

CENTER FOR DRUG EVALUATION AND RESEARCH

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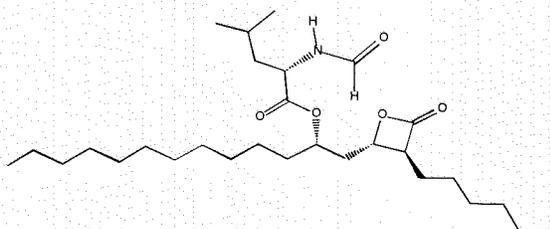
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XENICAL®
(orlistat)
CAPSULES

DESCRIPTION: XENICAL (orlistat) is a lipase inhibitor for obesity management that acts by inhibiting the absorption of dietary fats.

Orlistat is (S)-2-formylamino-4-methyl-pentanoic acid (S)-1-[[[(2S, 3S)-3-hexyl-4-oxo-2-oxetanyl] methyl]-dodecyl ester. Its empirical formula is $C_{29}H_{53}NO_5$, and its molecular weight is 495.7. It is a single diastereomeric molecule that contains four chiral centers, with a negative optical rotation in ethanol at 529 nm. The structure is:



Orlistat is a white to off-white crystalline powder. Orlistat is practically insoluble in water, freely soluble in chloroform, and very soluble in methanol and ethanol. Orlistat has no pK_a within the physiological pH range.

XENICAL is available for oral administration in dark-blue, hard-gelatin capsules, with light-blue imprinting. Each capsule contains 120 mg of the active ingredient, orlistat. The capsules also contain the inactive ingredients microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, povidone, and talc. Each capsule shell contains gelatin, titanium dioxide, and FD&C Blue No.1, with printing of pharmaceutical glaze NF, titanium dioxide, and FD&C Blue No.1 aluminum lake.

CLINICAL PHARMACOLOGY: Mechanism of Action: Orlistat is a reversible inhibitor of lipases. It exerts its therapeutic activity in the lumen of the stomach and small intestine by forming a covalent bond with the active serine residue site of gastric and pancreatic lipases. The inactivated enzymes are thus unavailable to hydrolyze dietary fat in the form of triglycerides into absorbable free fatty acids and monoglycerides. As undigested triglycerides are not absorbed, the resulting caloric deficit may have a positive effect on weight control. Systemic absorption of the drug is therefore not needed for activity. At the recommended therapeutic dose of 120 mg three times a day, orlistat inhibits dietary fat absorption by approximately 30%.

Pharmacokinetics: Absorption: Systemic exposure to orlistat is minimal. Following oral dosing with 360 mg ^{14}C -orlistat, plasma radioactivity peaked at approximately 8 hours; plasma concentrations of intact orlistat were near the limits of detection (<5 ng/mL). In therapeutic studies involving monitoring of plasma samples, detection of intact orlistat in plasma was sporadic and concentrations were low (<10 ng/mL or 0.02 μM), without evidence of accumulation, and consistent with minimal absorption.

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The average absolute bioavailability of intact orlistat was assessed in studies with male rats at oral doses of 150 and 1000 mg/kg/day and in male dogs at oral doses of 100 and 1000 mg/kg/day and found to be 0.12%, 0.59% in rats and 0.7%, 1.9% in dogs, respectively.

Distribution: In vitro orlistat was >99% bound to plasma proteins (lipoproteins and albumin were major binding proteins). Orlistat minimally partitioned into erythrocytes.

Metabolism: Based on animal data, it is likely that the metabolism of orlistat occurs mainly within the gastrointestinal wall. Based on an oral ¹⁴C-orlistat mass balance study in obese patients, two metabolites, M1 (4-member lactone ring hydrolyzed) and M3 (M1 with N-formyl leucine moiety cleaved), accounted for approximately 42% of total radioactivity in plasma. M1 and M3 have an open β-lactone ring and extremely weak lipase inhibitory activity (1000- and 2500-fold less than orlistat, respectively). In view of this low inhibitory activity and the low plasma levels at the therapeutic dose (average of 26 ng/mL and 108 ng/mL for M1 and M3, respectively, 2 to 4 hours after a dose), these metabolites are considered pharmacologically inconsequential. The primary metabolite M1 had a short half-life (approximately 3 hours) whereas the secondary metabolite M3 disappeared at a slower rate (half-life approximately 13.5 hours). In obese patients, steady-state plasma levels of M1, but not M3, increased in proportion to orlistat doses.

Elimination: Following a single oral dose of 360 mg ¹⁴C-orlistat in both normal weight and obese subjects, fecal excretion of the unabsorbed drug was found to be the major route of elimination. Orlistat and its M1 and M3 metabolites were also subject to biliary excretion. Approximately 97% of the administered radioactivity was excreted in feces; 83% of that was found to be unchanged orlistat. The cumulative renal excretion of total radioactivity was <2% of the given dose of 360 mg ¹⁴C-orlistat. The time to reach complete excretion (fecal plus urinary) was 3 to 5 days. The disposition of orlistat appeared to be similar between normal weight and obese subjects. Based on limited data, the half-life of the absorbed orlistat is in the range of 1 to 2 hours.

Special Populations: Because the drug is minimally absorbed, studies in special populations (geriatric, pediatric, different races, patients with renal and hepatic insufficiency) were not conducted.

Drug-Drug Interactions: Drug-drug interaction studies indicate that XENICAL had no effect on pharmacokinetics and/or pharmacodynamics of alcohol, digoxin, glyburide, nifedipine (extended-release tablets), oral contraceptives, phenytoin, or warfarin. XENICAL induced a modest increase of the bioavailability and lipid-lowering effect of pravastatin (see CLINICAL STUDIES and PRECAUTIONS). Alcohol did not affect the pharmacodynamics of orlistat.

Other Short-term Studies: In several studies of up to 6-weeks duration, the effects of therapeutic doses of XENICAL on gastrointestinal and systemic physiological processes were assessed in normal-weight and obese subjects. Postprandial cholecystokinin plasma concentrations were lowered after multiple doses of XENICAL in two studies but not significantly different from placebo in two other experiments. There were no clinically significant changes observed in gallbladder motility, bile composition or lithogenicity, or colonic cell proliferation rate, and no clinically significant reduction of gastric emptying time or gastric acidity. In addition, no effects on plasma triglyceride levels or systemic lipases were observed with the administration of XENICAL in these studies. In a 3-week study of 28 healthy male volunteers, XENICAL

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(120 mg three times a day) did not significantly affect the balance of calcium, magnesium, phosphorus, zinc, copper, and iron.

Dose-response Relationship: A simple maximum effect (E_{max}) model was used to define the dose-response curve of the relationship between XENICAL daily dose and fecal fat excretion as representative of gastrointestinal lipase inhibition. The dose-response curve demonstrated a steep portion for doses up to approximately 400 mg daily, followed by a plateau for higher doses. At doses greater than 120 mg three times a day, the percentage increase in effect was minimal.

CLINICAL STUDIES: Observational epidemiologic studies have established a relationship between obesity and visceral fat and the risks for cardiovascular disease, type 2 diabetes, certain forms of cancer, gallstones, certain respiratory disorders, and an increase in overall mortality. These studies suggest that weight loss, if maintained, may produce health benefits for obese patients who have or are at risk of developing weight-related comorbidities. The long-term effects of orlistat on morbidity and mortality associated with obesity have not been established.

The effects of XENICAL on weight loss, weight maintenance, and weight regain and on a number of comorbidities (eg, type 2 diabetes, lipids, blood pressure) were assessed in seven long-term (1- to 2-years duration) multicenter, double-blind, placebo-controlled clinical trials. During the first year of therapy, weight loss and weight maintenance were assessed. During the second year of therapy, some studies assessed continued weight loss and weight maintenance and others assessed the effect of orlistat on weight regain. These studies included over 2800 patients treated with XENICAL and 1400 patients treated with placebo. The majority of these patients had obesity-related risk factors and comorbidities. In these 7 studies, treatment with XENICAL and placebo designates treatment with XENICAL plus diet and placebo plus diet, respectively.

During the weight loss and weight maintenance period, a well-balanced, reduced-calorie diet that was intended to result in an approximate 20% decrease in caloric intake and provide 30% of calories from fat was recommended to all patients. In addition, all patients were offered nutritional counseling.

One-year Results: Weight Loss, Weight Maintenance, and Risk Factors: Weight loss was observed within 2 weeks of initiation of therapy and continued for 6 to 12 months.

Pooled data from five clinical trials indicated that the overall mean weight loss from randomization to the end of 6 months and 1 year of treatment in the intent-to-treat population were 12.4 lbs and 13.4 lbs in the patients treated with XENICAL and 6.2 lbs and 5.8 lbs in the placebo-treated patients, respectively. During the 4-week placebo lead-in period of the studies, an additional 5 to 6 lb weight loss was also observed in the same patients. Of the patients who completed 1 year of treatment, 57% of the patients treated with XENICAL (120 mg three times a day) and 31% of the placebo-treated patients lost at least 5% of their baseline body weight.

The percentages of patients achieving $\geq 5\%$ and $\geq 10\%$ weight loss after 1 year in five large multicenter studies for the intent-to-treat populations are presented in Table 1.

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Table 1. Percentage of Patients Losing $\geq 5\%$ and $\geq 10\%$ of Body Weight From Randomization After 1-Year Treatment*

Intent-to-Treat Population†								
Study No.	$\geq 5\%$ Weight Loss				$\geq 10\%$ Weight Loss			
	XENICAL n	Placebo n	p-value	XENICAL n	Placebo n	p-value		
14119B	35.5% 110	21.3% 108	0.021	16.4% 110	6.5% 108	0.022		
14119C	54.8% 343	27.4% 340	<0.001	24.8% 343	8.2% 340	<0.001		
14149	50.6% 241	26.3% 236	<0.001	22.8% 241	11.9% 236	0.02		
14161‡	37.1% 210	16.0% 212	<0.001	19.5% 210	3.8% 212	<0.001		
14185	42.6% 657	22.4% 223	<0.001	17.7% 657	9.9% 223	0.006		

The diet utilized during year 1 was a reduced-calorie diet.

* Treatment designates XENICAL 120 mg three times a day plus diet or placebo plus diet

† Last observation carried forward

‡ All studies, with the exception of 14161, were conducted at centers specialized in treating obesity and complications of obesity. Study 14161 was conducted with primary care physicians.

The relative changes in risk factors associated with obesity following 1 year of therapy with XENICAL and placebo are presented for the population as a whole and for the population with abnormal values at randomization.

Population as a Whole: The changes in metabolic, cardiovascular and anthropometric risk factors associated with obesity based on pooled data for five clinical studies, regardless of the patient's risk factor status at randomization, are presented in Table 2. One year of therapy with XENICAL resulted in relative improvement in several risk factors.

XENICAL® (orlistat)**Table 2. Mean Change in Risk Factors From Randomization Following 1-Year Treatment* Population as a Whole**

Risk Factor	XENICAL 120 mg†	Placebo†
Metabolic:		
Total Cholesterol	-2.0%	+5.0%
LDL-Cholesterol	-4.0%	+5.0%
HDL-Cholesterol	+9.3%	+12.8%
LDL/HDL	-0.37	-0.20
Triglycerides	+1.34%	+2.9%
Fasting Glucose, mmol/L	-0.04	+0.0
Fasting Insulin, pmol/L	-6.7	+5.2
Cardiovascular:		
Systolic Blood Pressure, mm Hg	-1.01	+0.58
Diastolic Blood Pressure, mm Hg	-1.19	+0.46
Anthropometric:		
Waist Circumference, cm	-6.45	-4.04
Hip Circumference, cm	-5.31	-2.96

* Treatment designates XENICAL 120 mg three times a day plus diet or placebo plus diet

† Intent-to-treat population at week 52, observed data based on pooled data from 5 studies

Population With Abnormal Risk Factors at Randomization: The changes from randomization following 1-year treatment in the population with abnormal lipid levels (LDL \geq 130 mg/dL, LDL/HDL \geq 3.5, HDL $<$ 35 mg/dL) were greater for XENICAL compared to placebo with respect to LDL-cholesterol (-7.83% vs +1.14%) and the LDL/HDL ratio (-0.64 vs -0.46). HDL increased in the placebo group by 20.1% and in the XENICAL group by 18.8%. In the population with abnormal blood pressure at baseline (systolic BP \geq 140 mm Hg), the change in SBP from randomization to 1 year was greater for XENICAL (-10.89 mm Hg) than placebo (-5.07 mm Hg). For patients with a diastolic blood pressure \geq 90 mm Hg, XENICAL patients decreased by -7.9 mm Hg while the placebo patients decreased by -5.5 mm Hg. Fasting insulin decreased more for XENICAL than placebo (-39 vs -16 pmol/L) from randomization to 1 year in the population with abnormal baseline values (\geq 120 pmol/L). A greater reduction in waist circumference for XENICAL vs placebo (-7.29 vs -4.53 cm) was observed in the population with abnormal baseline values (\geq 100 cm).

Effect on Weight Regain: Three studies were designed to evaluate the effects of XENICAL compared to placebo in reducing weight regain after a previous weight loss achieved following either diet alone (one study, 14302) or prior treatment with XENICAL (two studies, 14119C and 14185). The diet utilized during the 1-year weight regain portion of the studies was a weight-maintenance diet, rather than a weight-loss diet, and patients received less nutritional counseling than patients in weight-loss studies. For studies 14119C and 14185, patients' previous weight loss was due to 1 year

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of treatment with XENICAL in conjunction with a mildly hypocaloric diet. Study 14302 was conducted to evaluate the effects of 1 year of treatment with XENICAL on weight regain in patients who had lost 8% or more of their body weight in the previous 6 months on diet alone.

In study 14119C, patients treated with placebo regained 52% of the weight they had previously lost while the patients treated with XENICAL regained 26% of the weight they had previously lost ($p < 0.001$). In study 14185, patients treated with placebo regained 63% of the weight they had previously lost while the patients treated with XENICAL regained 35% of the weight they had lost ($p < 0.001$). In study 14302, patients treated with placebo regained 53% of the weight they had previously lost while the patients treated with XENICAL regained 32% of the weight that they had lost ($p < 0.001$).

Two-year Results: Long-term Weight Control and Risk Factors: The treatment effects of XENICAL were examined for 2 years in four of the five 1-year weight management clinical studies previously discussed (see Table 1). At the end of year 1, the patients' diets were reviewed and changed where necessary. The diet prescribed in the second year was designed to maintain patient's current weight. XENICAL was shown to be more effective than placebo in long-term weight control in four large, multicenter, 2-year double-blind, placebo-controlled studies.

Pooled data from four clinical studies indicate that 40% of all patients treated with 120 mg three times a day of XENICAL and 24% of patients treated with placebo who completed 2 years of the same therapy had $\geq 5\%$ loss of body weight from randomization. Pooled data from four clinical studies indicate that the relative weight loss advantage between XENICAL 120 mg three times a day and placebo treatment groups was the same after 2 years as for 1 year, indicating that the pharmacologic advantage of XENICAL was maintained over 2 years. In the same studies cited in the *One-year Results* (see Table 1), the percentages of patients achieving a $\geq 5\%$ and $\geq 10\%$ weight loss after 2 years are shown in Table 3.

Table 3. Percentage of Patients Losing $\geq 5\%$ and $\geq 10\%$ of Body Weight From Randomization After 2-Year Treatment*

Study No.	Intent-to-Treat Population**							
	$\geq 5\%$ Weight Loss				$\geq 10\%$ Weight Loss			
	XENICAL n	Placebo n	p-value	XENICAL n	Placebo n	p-value		
14119C	45.1% 133	23.6% 123	<0.001	24.8% 133	6.5% 123	<0.001		
14149	43.3% 178	27.2% 158	0.002	18.0% 178	9.5% 158	0.025		
14161†	25.0% 148	15.0% 113	0.049	16.9% 148	3.5% 113	0.001		
14185	34.0% 147	27.9% 122	0.279	17.7% 147	11.5% 122	0.154		

The diet utilized during year 2 was designed for weight maintenance and not weight loss.

* Treatment designates XENICAL 120 mg three times a day plus diet or placebo plus diet

** Last observation carried forward

† All studies, with the exception of 14161 were conducted at centers specializing in treating obesity or complications of obesity. Study 14161 was conducted with primary care physicians.

The relative changes in risk factors associated with obesity following 2 years of therapy were also assessed in the population as a whole and the population with abnormal risk factors at randomization.

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Population as a Whole: The relative differences in risk factors between treatment with XENICAL and placebo were similar to the results following 1 year of therapy for total cholesterol, LDL-cholesterol, LDL/HDL ratio, triglycerides, fasting glucose, fasting insulin, diastolic blood pressure, waist circumference, and hip circumference. The relative differences between treatment groups for HDL cholesterol and systolic blood pressure were less than that observed in the year one results.

Population With Abnormal Risk Factors at Randomization: The relative differences in risk factors between treatment with XENICAL and placebo were similar to the results following 1 year of therapy for LDL- and HDL-cholesterol, triglycerides, fasting insulin, diastolic blood pressure, and waist circumference. The relative differences between treatment groups for LDL/HDL ratio and isolated systolic blood pressure were less than that observed in the year one results.

Study of Patients With Type 2 Diabetes: A 1-year double-blind, placebo-controlled study in type 2 diabetics (N=321) stabilized on sulfonylureas was conducted. Thirty percent of patients treated with XENICAL achieved at least a 5% or greater reduction in body weight from randomization compared to 13% of the placebo-treated patients ($p<0.001$). Table 4 describes the changes over 1 year of treatment with XENICAL compared to placebo, in sulfonylurea usage and dose reduction as well as in hemoglobin HbA1c, fasting glucose, and insulin.

Table 4. Mean Changes in Body Weight and Glycemic Control From Randomization Following 1-Year Treatment in Patients With Type 2 Diabetes

	XENICAL 120 mg* (n=162)	Placebo* (n=159)	Statistical Significance
% patients who discontinued dose of oral sulfonylurea	11.7%	7.5%	†
% patients who decreased dose of oral sulfonylurea	31.5%	21.4%	†
Average reduction in sulfonylurea medication dose	-22.8%	-9.1%	†
Body weight change (lbs)	-8.9	-4.2	†
HbA1c	-0.18%	+0.28%	†
Fasting glucose, mmol/L	-0.02	+0.54	†
Fasting insulin, pmol/L	-19.68	-18.02	ns

Statistical significance based on intent-to-treat population, last observation carried forward.

* Treatment designates XENICAL 120 mg three times a day plus diet or placebo plus diet.

† Statistically significant ($p\leq 0.05$) based on intent-to-treat, last observation carried forward.

ns nonsignificant, $p>0.05$

In addition, XENICAL (n=162) compared to placebo (n=159) was associated with significant lowering for total cholesterol (-1.0% vs +9.0%, $p\leq 0.05$), LDL-cholesterol (-3.0% vs +10.0%, $p\leq 0.05$), LDL/HDL ratio (-0.26 vs -0.02, $p\leq 0.05$) and triglycerides (+2.54% vs +16.2%, $p\leq 0.05$), respectively. For HDL cholesterol, there was a +6.49% increase on XENICAL and +8.6% increase on placebo, $p>0.05$. Systolic blood pressure increased by +0.61 mm Hg on XENICAL and increased by +4.33 mm Hg on placebo,

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p>0.05. Diastolic blood pressure decreased by -0.47 mm Hg for XENICAL and by -0.5 mm Hg for placebo, p>0.05.

Glucose Tolerance in Obese Patients: Two-year studies that included oral glucose tolerance tests were conducted in obese patients not previously diagnosed or treated for type 2 diabetes and whose baseline oral glucose tolerance test (OGTT) status at randomization was either normal, impaired, or diabetic.

The progression from a normal OGTT at randomization to a diabetic or impaired OGTT following 2 years of treatment with XENICAL (n=251) or placebo (n=207) were compared. Following treatment with XENICAL, 0.0% and 7.2% of the patients progressed from normal to diabetic and normal to impaired, respectively, compared to 1.9% and 12.6% of the placebo treatment group, respectively.

In patients found to have an impaired OGTT at randomization, the percent of patients improving to normal or deteriorating to diabetic status following 1 and 2 years of treatment with XENICAL compared to placebo are presented. After 1 year of treatment, 45.8% of the placebo patients and 73% of the XENICAL patients had a normal oral glucose tolerance test while 10.4% of the placebo patients and 2.6% of the XENICAL patients became diabetic. After 2 years of treatment, 50% of the placebo patients and 71.7% of the XENICAL patients had a normal oral glucose tolerance test while 7.5% of placebo patients were found to be diabetic and 1.7% of XENICAL patients were found to be diabetic after treatment.

INDICATIONS AND USAGE: XENICAL is indicated for obesity management including weight loss and weight maintenance when used in conjunction with a reduced-calorie diet. XENICAL is also indicated to reduce the risk for weight regain after prior weight loss. XENICAL is indicated for obese patients with an initial body mass index (BMI) ≥ 30 kg/m² or ≥ 27 kg/m² in the presence of other risk factors (e.g., hypertension, diabetes, dyslipidemia).

Table 5 illustrates body mass index (BMI) according to a variety of weights and heights. The BMI is calculated by dividing weight in kilograms by height in meters squared. For example, a person who weighs 180 lbs and is 5'5" would have a BMI of 30.

Table 5. Body Mass Index (BMI), kg/m²*

HEIGHT (ft)	WEIGHT (lb)																				
	120	130	140	150	160	170	180	190	200	210	220	230	240	250	260	270	280	290	300	310	320
4'10"	25	27	29	31	34	36	38	40	42	44	46	48	50	52	54	57	59	61	63	65	67
4'11"	24	26	28	30	32	34	36	38	40	43	45	47	49	51	53	55	57	59	61	63	65
5'0"	23	25	27	29	31	33	35	37	39	41	43	45	47	49	51	53	55	57	59	61	63
5'1"	23	25	27	28	30	32	34	36	38	40	42	44	45	47	49	51	53	55	57	59	61
5'2"	22	24	26	27	29	31	33	35	37	38	40	42	44	46	48	49	51	53	55	57	59
5'3"	21	23	25	27	28	30	32	34	36	37	39	41	43	44	46	48	49	51	53	55	57
5'4"	21	22	24	26	28	29	31	33	34	36	38	40	41	43	44	46	48	50	51	53	55
5'5"	20	22	23	25	27	28	30	32	33	35	37	38	40	42	43	45	47	48	50	52	53
5'6"	19	21	23	24	26	27	29	31	32	34	36	37	39	40	42	43	45	47	48	50	52
5'7"	19	20	22	24	25	27	28	30	31	33	35	36	38	39	41	42	44	45	47	49	50
5'8"	18	20	21	23	24	26	27	29	30	32	34	35	37	38	40	41	43	44	46	47	49
5'9"	18	19	21	22	24	25	27	28	30	31	33	34	36	37	38	40	41	43	44	46	47
5'10"	17	19	20	22	23	24	26	27	29	30	32	33	35	36	37	39	40	42	43	45	46

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5'11"	17	18	20	21	22	24	25	27	28	29	31	32	34	35	36	38	39	41	42	43	45
6'0"	16	18	19	20	22	23	24	26	27	29	30	31	33	34	35	37	38	39	41	42	43
6'1"	16	17	19	20	21	22	24	25	26	28	29	30	32	33	34	36	37	38	40	41	42
6'2"	15	17	18	19	21	22	23	24	26	27	28	30	31	32	33	35	36	37	39	40	41

* Conversion Factors:

Weight in lbs ÷ 2.2 = weight in kilograms (kg)

Height in inches × 0.0254 = height in meters (m)

1 foot = 12 inches

CONTRAINDICATIONS: XENICAL is contraindicated in patients with chronic malabsorption syndrome or cholestasis, and in patients with known hypersensitivity to XENICAL or to any component of this product.

WARNINGS: Miscellaneous: Organic causes of obesity (e.g., hypothyroidism) should be excluded before prescribing XENICAL.

PRECAUTIONS: General: Patients should be advised to adhere to dietary guidelines (see DOSAGE AND ADMINISTRATION). Gastrointestinal events (see ADVERSE REACTIONS) may increase when XENICAL is taken with a diet high in fat (>30% total daily calories from fat). The daily intake of fat should be distributed over three main meals. If XENICAL is taken with any one meal very high in fat, the possibility of gastrointestinal effects increases.

Patients should be counseled to take a multivitamin supplement that contains fat-soluble vitamins to ensure adequate nutrition because XENICAL has been shown to reduce the absorption of some fat-soluble vitamins and beta-carotene. In addition, the levels of vitamin D and beta-carotene may be low in obese patients compared with non-obese subjects. The supplement should be taken once a day at least 2 hours before or after the administration of XENICAL, such as at bedtime.

Table 6 illustrates the percentage of patients on XENICAL and placebo who developed a low vitamin level on two or more consecutive visits during 1 and 2 years of therapy in studies in which patients were not previously receiving vitamin supplementation.

Table 6. Incidence of Low Vitamin Values on Two or More Consecutive Visits (Nonsupplemented Patients With Normal Baseline Values - First and Second Year)

	Placebo*	XENICAL*
Vitamin A	1.0%	2.2%
Vitamin D	6.6%	12.0%
Vitamin E	1.0%	5.8%
Beta-carotene	1.7%	6.1%

* Treatment designates placebo plus diet or XENICAL plus diet